A CASE OF GRANISETRON ASSOCIATED INTRAOPERATIVE CARDIAC ARREST

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We report a case of intraoperative severe bradycardia that resulted in asystole and cardiac arrest shortly after (<2 min) intravenous granisetron 1mg for postoperative nausea and vomiting prophylaxis, that occurred in a female patient who underwent an elective total thyroidectomy. After two cycles of cardiopulmonary resuscitation and defibrillation, spontaneous circulation and sinus rhythm returned successfully. Postoperatively, the patient was diagnosed with a drug-induced long QT syndrome. At the time of the event, granisetron was the only medication administered. Furthermore, there was no reason to suspect electrolyte abnormalities. We explore the association of the onset of severe sinus bradycardia with the intravenous administration of granisetron.

Keywords: Antiemetics, complications, cardiac arrest

Introduction

The 5 Hydroxytryptamine type 3 (5-HT3) serotonin receptor antagonists are widely used in the treatment of postoperative (PONV) and chemotherapy induced nausea and vomiting (CINV). Even though its clinical safety has been established in many trials, they have the ability to block human cardiac sodium and potassium channels which may cause adverse cardiac effects and may predispose to cardiac dysrhythmias1,2. Labeling for some of the currently approved 5-HT3 antagonists indicates the potential for cardiac adverse events, primarily prolongation of the QT interval but also other changes of electrocardiogram (ECG) intervals3,4.

Cardiac dysrhythmias have been reported with 5-HT3 antagonists during the perioperative period, especially with ondansetron and dolasetron including ventricular or supraventricular tachycardia, premature ventricular contractions, atrial fibrillation, coronary vasospasm with chest pain and intraoperative pulseless ventricular tachycardia5-10. Furthermore, similar adverse events have been reported in cancer patients under chemotherapy11,12.

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In October 2009, labeling of granisetron (Kytril; Roche Laboratories, Basel, Switzerland) was changed to include a warning for precautionary use in patients potentially vulnerable to QT prolongation. In 2010 and 2011, the US Food and Drug Administration (FDA) required the withdrawal of intravenous (IV) dolasetron for the treatment of CINV due to cardiac safety concerns and expanded warnings in labeling regarding potential cardiac safety issues with ondansetron and granisetron.

Although small clinical trials with IV granisetron have not found any significant changes in QT intervals, individual reports of QT prolongation have been published. It is important to note that concerning granisetron, a thorough QT study has not yet conducted. However, no published case reports of severe cardiac events were reported with granisetron as the suspect agent. We report a case of intraoperative severe bradycardia that resulted in asystole and cardiac arrest after IV granisetron 1mg for PONV prophylaxis, occurred in a female patient who underwent an elective total thyroidectomy.

Consent for publication

Patient has given written consent for publication

Case Description

A 50 year old morbidly obese female (104kg, 150cm, BMI 46.2), ASA II, was admitted to our tertiary university hospital for an elective total thyroidectomy. Past medical history included seven pregnancies, hyperthyroidism and psychosis diagnosed one year ago. Upon admission to the hospital, the patient reported no known medication allergies. At the time of first diagnosis, cardiac echocardiography showed normal and 12-lead electrocardiogram (ECG) showed mild left ventricular hypertrophy (LVH) and borderline QT prolongation (QTc 459ms). Initial daily drug therapy regimen included methimazole 30mg, propranolol 80mg and risperidone 4mg. Four months later the patient visited the pre-anesthesia clinic and was evaluated. Thyroid function and psychological status were normal. A 12-lead ECG showed similar borderline QT prolongation (QTc 452ms). Her daily therapy regimen included methimazole 15mg, propranolol 40mg and sulpiride 100mg.

On the day of surgery patient came to operating room without changes with preoperative evaluation. Induction in anesthesia included midazolam 1mg, fentanyl 100 mcg, propofol 200mg and rocuronium 60mg. During maintenance with oxygen, nitrous oxide and sevoflurane 2%, dexamethasone 8mg, morphine 5mg and paracetamol 1000mg were administered. Throughout surgery, the patient’s heart was in normal sinus rhythm. Towards the end of the procedure patient received IV granisetron 1mg for PONV prophylaxis. Then, in less than 2min patient developed severe sinus bradycardia (<30 beats/min). Atropine 0.6mg was given immediately and pushed with 20 ml of normal saline. Bradycardia resulted in asystole and cardiopulmonary resuscitation (CPR) was initiated immediately. After one cycle of CPR sinus rhythm presented for a few seconds and then converted to ventricular fibrillation (VF). One shock 200J delivered and a second cycle of CPR started and epinephrine 1mg was given. CPR resulted in return of spontaneous circulation and sinus rhythm. Total CPR duration was 6 minutes. Arterial blood gases showed: PH 7.221, PaCO2 61mmHg, PaO2 232 mmHg, Hb 13 g/dl, with normal blood sugar and electrolytes (Na+, K+, Ca++) within normal limits. A 12-lead ECG showed sinus rhythm and substantial QT prolongation (QTc 494ms). Patient was then extubated, recovered uneventfully and was transferred to cardiac ICU. Cardiac CT angiography showed mild non obstructive coronary artery disease and mild LVH. Cardiologists decided that the patient indicated a high likelihood of drug-induced long QT-syndrome (LQTS). One week later they proceeded with right ventricle intracardiac device implantation for secondary prevention for VF arrest and long QT. Transthoracic echocardiography with contrast showed only mild LVH and patient was discharged. About 3 months later 12-lead ECG showed sinus rhythm with 1st degree atrioventricular block and normal QT interval (QTc 381ms).

Discussion

It is clear that very shortly (<2min) after the IV administration of granisetron 1mg for PONV
prophylaxis, our patient developed severe sinus bradycardia which eventually resulted in asystole and cardiac arrest. To the best of our knowledge this is the first case with granisetron in a dose for PONV prophylaxis, to be associated with intraoperative cardiac arrest. However, we cannot conclusively establish granisetron as the cause. The patient was incidentally taking propranolol for her daily therapy regimen which probably contributed to cardiac conduction abnormalities and to sinus bradycardia. Additionally, the patient was in antipsychotic drug therapy with sulpiride, associated with QT prolongation\textsuperscript{17-19}. This emphasizes the importance of drug-drug interactions in the perioperative setting\textsuperscript{2}. However, at the time of the event, granisetron was the only medication administered. Furthermore, there was no reason to suspect electrolyte abnormalities in predisposing to this event. Nonetheless, it is logical in this case to explore the association of the onset of severe sinus bradycardia with the intravenous administration of granisetron. The non-significant past medical history, as well as the timing of administration of other medications, support our concern.

The QT interval is the ECG manifestation of ventricular depolarization and repolarization. The RR interval preceding the QT interval is measured for rate correction (QTc). Although there is no consensus about QTc normal values, most agree that QTc intervals $<440$ ms are clearly normal and intervals of 440-460 ms in men and 440-470 ms in women are considered borderline\textsuperscript{19,20}. Preoperatively our patient presented a borderline QT prolongation (QTc 452ms), while in the immediate postoperative period experienced a substantial QT prolongation (QTc 494ms). However, recent study showed that postoperative QTc-interval prolongation is common\textsuperscript{21}. Several perioperatively administered drugs were associated with a substantial QT-interval prolongation and drug-drug interactions appeared to be a major contributing factor to postoperative QTc-prolongation\textsuperscript{21}. The authors emphasized that the exact cause of postoperative QTc-prolongation and its clinical relevance, remain unclear\textsuperscript{21}.

Drug-induced long QT syndrome (LQTS) is characterized by acquired QT interval prolongation and increased risk of torsade de pointes (TdP)\textsuperscript{19,20}. In our patient after the first cycle of CPR sinus rhythm appeared for a few seconds and then was converted to VF. However, there is no adequate evidence that TdP was an intermediate dysrhythmia. The fact that 3 months after the event our patient presented with normal QT interval (QTc 381ms) rather confirms a drug-induced LQTS. QT prolongation and TdP are the most common reasons pharmaceuticals are restricted from the US market\textsuperscript{22}.

In our patient the exact cause of the onset of this severe intraoperative sinus bradycardia, which resulted in asystole is not clear. Multiple QT prolonging drugs (granisetron, propranolol and sulpiride) may be an evident explanation\textsuperscript{18}. Granisetron has been shown to block human cardiac sodium channels, which may lead to clinically relevant sodium channel block. Sodium channel blockade is associated with QRS widening, which may predispose to cardiac dysrhythmias. Furthermore, granisetron possesses affinity for the potassium channels, which may prolong repolarization. The complexity of cardiovascular responses produced by 5-hydroxytryptamine, include heterogeneous, unpredictable and conflicting effects leading to bradycardia or tachycardia, hypotension or hypertension, and vasodilatation or vasoconstriction\textsuperscript{23}. This has been explained by the capability of this monoamine to interact with different receptors in the central nervous system, the autonomic ganglia and postganglionic nerve endings, the vascular smooth muscle and endothelium, and the cardiac tissue\textsuperscript{23}.

The prevailing point of view is that inhibition of 5-HT\textsubscript{3} receptors in the heart could lead to unopposed action of other serotonin receptors leading to tachyarrhythmias as described in the literature\textsuperscript{2-8}. Postulated mechanism in animal studies, included inhibition of Bezold-Jarisch like cardiac reflex and coronary vasoconstriction\textsuperscript{23}. However, this has not been yet established in humans. Actually, our patient experienced severe sinus bradycardia which resulted to cardiac arrest, instead of tachyarrythmia. Three other cases have been reported with severe sinus bradycardia (<30beats/min) after IV administration of ondansetron during induction in anesthesia, associated with respiratory arrest and loss of consciousness\textsuperscript{24-25}. Theoretically, the inhibition of 5-HT\textsubscript{3} receptors may also lead to bradycardia, mediated by unopposed
activation of 5-HT(1A) receptors on the ground of drug-induced long QTS\textsuperscript{23}.

It seems that so far we miss the whole picture of drug interactions with the perioperative use of the 5-HT3 antagonists. This means that further in depth research is required. It is important that anesthesiologists should be vigilant of rare but potentially life-threatening cardiovascular compromise induced by these medications. As cardiac dysrhythmias have been reported with 5-HT3 antagonists, it is inevitable that as their utilization in the perioperative setting increases, the frequency of such reports will increase.

References

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